Bibliography and Epitome

VOL. 27 AM. J. ORTHOPSYCHIAT. APRIL, 1957

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Frontal Lobotomy 1936–1956

Three thousand lobotomy patients have been compared in 3 different categories: (1) Prefrontal lobotomy versus transorbital lobotomy; (2) private patients versus state hospital patients; (3) according to personality reaction type, schizophrenic, affective and psychoneurotic.

Follow-up studies reveal that following prefrontal lobotomy some 70 per cent. of schizophrenics, 80 per cent. of affectives, and 90 per cent. of psychoneurotics are functioning outside of the hospital in the 5- to 10-year period. This figure is twice as high in private patients as it is in state hospital patients.

Transorbital lobotomy is safer, more effective (with the exception of the hallucinated schizophrenic patients), and far more applicable to the problem of the state hospital, than is prefrontal lobotomy.

Multiple operations have been performed in about 1 patient in 10, with eventual satisfactory results in a third of them. When it is considered that this fraction amounts to 100 patients out of the hospital, this figure acquires significance.

Hospitals that select patients for operation with a view to release, and that encourage the relatives of patients to participate actively in the management of convalescence, enjoy a much higher percentage of released patients than do those that employ lobotomy more for the control of disturbed behaviour.

(Author's Abstr.)

Psychotomimetics, Clinical and Theoretical Considerations: Harmine, Win-2299 and Nalline

Harmine, Win-2299, and Nalline in single dosage produce many new mental effects in schizophrenics grossly similar to those elicited by mescaline and LSD. Many of the same effects are reported in normals after Harmine and Nalline (other workers). Unlike mescaline and LSD at usual dosage levels, the present psychotomimetics regularly produce drowsiness and sleep along with the aberrant mental effects. The resultant state is partly that of "hypnagogic" visual hallucinations or imagery. The results with increased dosage suggest that the basic effect of these agents is to produce an acute toxic reaction type. The difference between them and mescaline or LSD with respect to clouding of consciousness and certain aspects of the hallucinogenic response may be quantitative rather than qualitative. The indole nucleus is not necessary in the structure of psychotomimetics since Win-2299 and Nalline are non-indoles. The tertiary nitrogen grouping may contribute to certain aspects of psychotomimetic action.

(Authors' Abstr.)

MAY

JUNE

Studies on the Diethylamide of Lysergic Acid (LSD-25)

1. Chlorpromazine ameliorates partially the abnormal mental state induced by the diethylamide of lysergic acid (LSD-25) in man. Chlorpromazine has this effect when administered before or after LSD.

2. Azacyclonol (Frenquel) does not reduce the intensity of the LSD psychosis in man.

3. Reserpine does not mitigate the LSD psychosis in man. Patients receiving a combination of reserpine and LSD have severer symptoms than when receiving either drug alone. (Authors' Abstr.)

Studies on Phenylketonuria

Young phenylketonuric children frequently have seizures, usually in the form of infantile spasms. In that age group, hypsarhythmia and multiple seizure foci are found on electroencephalography. As these children grow older, they may have tonic-clonic convulsions, and their EEGs tend to show focal or generalized spike discharges. Of 23 patients, 7 had spike-and-

wave complexes that were similar to those found in petit mal epilepsy. Only one adult had normal EEGs.

EEG patterns vary with age regardless of etiology.

Eight patients undergoing treatment with phenylalanine-restricted diet had EEG examinations. Five of these showed an EEG improvement on the diet; two in this group showed increasingly abnormal EEGs when treatment was interrupted. In two other children no remarkable EEG changes could be noted. The eighth patient had only one EEG recorded.

These studies suggest that the phenylalanine-restricted diet has beneficial effect on seizures and EEGs of phenylketonuric children. A warning of caution against over-interpretation should be sounded, however, because EEGs will change with age, with stage of waking, drowsiness, and sleep, and only EEGs obtained under very similar conditions should be compared.

(Authors' Abstr.)

Conversion of Adrenaline to Adrenolutin in Human Blood Serum

Adrenochrome (3-hydroxy-N-methyl-5,6-dioxoindole) and adrenolutin (3,5,6,-trihydroxy-1-methylindole) may be involved in the production of schizophrenia. These compounds have not been detected in blood, nor have enzyme systems been clearly demonstrated which can produce them from adrenaline. It is therefore of interest to show that the conversion can occur in blood serum.

Following Osmond and Smythies' suggestion that schizophrenic patients may have within them an M substance related in structure to both mescaline and epinephrine, Hoffer, Osmond, and Smythies discovered that adrenochrome, an oxidized derivative of epinephrine, induced psychological changes in humans. Hoffer and Osmond postulated that the basic physiological abnormality in schizophrenia was an abnormality in the autonomic nervous system expressed chemically in the increased production of both acetylcholine and some oxidized derivative of adrenaline similar in structure to either adrenochrome or adrenolutin. Both these substances have similar properties in producing psychological changes.

The presence of both adrenochrome and adrenolutin in human blood serum has not been demonstrated, although enzyme systems that could achieve this conversion are known. Recently, Leach and Heath demonstrated that epinephrine added to schizophrenic serum was rapidly converted to a new substance having an absorption peak at 395 mμ. To a less degree the same conversion occurred in normal blood. The degree of conversion was significantly greater in schizophrenic serum than in normal serum. The conversion was accelerated by the addition of copper ions and inhibited by the addition of cyanide. They therefore believe that the enzyme is a copper-containing phenolase, similar to tyrosinase. When adrenochrome was added to serum, it was even more quickly converted to the new substance.

Adrenolutin, a reduced derivative of adrenochrome, might be more stable in a reducing medium such as serum, which contains ascorbic acid, glutathione, and proteins rich in sulfhydryl groups. Adrenolutin was therefore added to serum following in detail the procedure of Leach and Heath.

The absorption curve obtained with adrenolutin after 1 minute is similar to the one obtained by incubating epinephrine in schizophrenic blood for 80 minutes. After 80 minutes there is little change in the curve. This suggests that the substance formed in blood serum from adrenaline is adrenolutin.

In conclusion, it has been found that the enzyme which, according to Leach and Heath, occurs in higher concentration in schizophrenic than in normal blood, converts adrenaline to adrenolutin. This reinforces the suggestion that this oxidized derivative may play a role in the production of schizophrenia.

(Authors' Abstr.)

Lysergic Acid Diethylamide (LSD-25) Antagonists

Crude brain extract up to concentrations of 2 mg. per cubic centimeter of the mixture does not essentially change the behaviour of the Siamese fighting fish.

If the fish are allowed to remain in contact with this concentration of crude brain extract for two hours, addition of LSD-25 (2 γ per cubic centimeter) does not have its usual effect.

Whereas 0·02 and 0·2 mg. of crude brain extract per cubic centimeter have a minor effect on the LSD reaction, 2 mg. of crude brain extract per cubic centimeter blocks the LSD reaction. The LSD reaction observed corresponds to a concentration of 0·2 γ of LSD per cubic centimeter.

If the blocking effect occurs within the fish, this is apparently the first time that blocking action (not a symptomatic depressant) of behaviour changes engendered by LSD has been produced by a biologically derived substance.

(Authors' Abstr.)

MAY

A Working Hypothesis as to the Nature of Hypnosis

"Animal hypnosis" (Totstellreflex), which represents one of the basic types of reactions common to man and animals, was used as an experimental pathogenetic model for the study of the mechanism of several psychiatric syndromes (catatonia, hypnoid syndrome, etc.). The course of this reaction in phylogenesis and ontogenesis was studied, and an EEG analysis was made in the rabbit.

"Animal hypnosis" is paroxysmally initiated central inhibition, which originates in the subcortical regions of the brain and from there spreads to the cerebral hemispheres. The termination of this state is realized by the ascending reticular activating system (Magoun), the function of which is not impaired in the course of "animal hypnosis".

The susceptibility of this paroxysmal inhibition to react to certain stimuli decreases in the course of ontogenesis. The same applies to the phylogenetic development of vertebrates with the neocortex. It follows that the old mechanism of "animal hypnosis", which is localized in the brain stem, is dominated during evolution more and more by younger cortical mechanisms, which progressively displace the reaction of paroxysmal inhibition from the normal animal's behaviour and finally lead to its disappearance.

The opinion is expressed that the reaction of "animal hypnosis"—paroxysmal inhibition —appears in higher evolutionary forms only in the case that normal subordination interrelations of individual parts of the brain are disturbed to such an extent that old, preformed mechanisms of the brain stem, which are inhibited under normal conditions by younger functional structures, come into play or become manifest. Such a situation occurs only under pathological conditions, and that is the reason that "animal hypnosis" in higher evolutionary forms and in man must be considered to be a pathological reaction, an instinctive, phylogenetically preformed mechanism, which appears in regressive forms of behaviour.

(Author's Abstr.)

JUNE

VOL. 78 JULY, 1957

The Incidence of Ammon's Horn Sclerosis

The findings of the present investigation and the interpretation placed upon them may be summarized as follows:

1. Out of 65 cases, selected only to avoid those patients with chronic organic disease of the brain, 5 (8 per cent.) showed lesions of the Ammon's horns all of which were of recent onset. These were considered in each case to be related to terminal disease or to the development of severe hypoxia in the hours or days before death. In none of the 65 cases was Ammon's horn sclerosis found, and there was no evidence to suggest that this could be looked on as a common (or indeed as an uncommon) incidental finding.

2. It was again confirmed that of those cases with organic disease of the brain the incidence of Ammon's horn lesions was essentially confined to the arteriosclerotic and the senile groups (including Alzheimer's disease) and to cases of general paresis, although very few cases of this were examined.

3. The incidence of lesions in the group of epileptic patients was roughly the same as that in the senile and the arteriosclerotic groups, but differences both in the morphological appearances of the lesions and in the mechanism of their production, in so far as this is known, suggest that such lesions should not be grouped together indiscriminately. In the senile and arteriosclerotic cases the development of the lesion occurs during the last few years of life and is found in the presence of severe, widespread degenerative changes occurring throughout the brain.

In the senile these seem to be part of a generalized disintegration of cerebral tissue (although there is no explanation why this should be so strikingly intense in the hippocampus). In the arteriosclerotic the lesion is that of infarction related to vascular disease. Since, how-

ever, vascular change plays a part in the senile process no single explanation is likely to be adequate.

4. In the adult cases of cryptogenic epilepsy the appearances are constantly those of a lesion of some considerable duration, and the evidence supports the view that this originates as the result of anoxia occurring in the early years of life, either as a birth injury or as the result of some upset in early childhood. Since convulsions, however, may themselves result in severe hypoxia they alone may account for the presence of a lesion.

(Author's Abstr.)

JUNE

Procedures Changing the Carbonic Anhydrase Activity of the Central Nervous System

The results of attempts to change the carbonic anhydrase content of the brain are given.

Zinc salts, when given either parenterally or orally, failed to increase carbonic anhydrase in the brain of adult rats, nurslings or of the young mothers treated during pregnancy.

Alcohol feedings did not decrease carbonic anhydrase in rat brain.

Attempts to increase carbonic anhydrase in the brains of growing rats with carbon dioxide were negative except in one instance in which normal growth occurred during treatment.

Forced blood production by simulated altitude resulted in increases in carbonic anhydrase in the cerebellum and cerebrum of rats after a 65 day exposure.

Bone marrow caused a rostral progression of increase in carbonic anhydrase in growing rats in which the brain stem, cerebellum and cerebrum were tested.

Results similar to those with bone marrow were found with the use of chlorpromazine.

Large increases in carbonic anhydrase eventually occurred in the kidney with injections of both bone marrow and chlorpromazine.

Electric shock in guinea pigs reduced the carbonic anhydrase in those parts of the brain more directly between the electrodes.

The possible significance of the positive findings is discussed.

(Authors' Abstr.)

VOL. 60 **FOL. PSYCHIAT. NEUR. NEUROCHIR. NEERL.** FEBRUARY, 1957

VOL. 9 **EEG CLIN. NEUROPHYSIOL.** MAY, 1957

The Entorhinal Area; Electrophysiological Studies of its Interrelations with Rhinencephalic Structures and the Brainstem

1. Electrophysiological investigations have been performed in the rhinencephalon of 16 specimens of the marsupial phalanger (Trichosurus vulpecula).

2. The reciprocity of pathways between entorhinal area, hippocampus and fornix was tested. It was found that whereas stimulation of the fornix was followed by responses in both the hippocampus and entorhinal area, stimulation of the entorhinal area evoked responses in the hippocampus, but only small irregular responses in the fornix. The findings on entorhinal stimulation thus throw some doubt on the classical concepts of Papez (1937) of major projections from entorhinal area to fornix through the hippocampal formation.

3. Interaction patterns were studied in the hippocampal responses following paired stimuli to fornix and entorhinal area. It was found that a conditioning stimulus to the fornix inhibited the test response to entorhinal stimulation. Conversely, a conditioning stimulus to the entorhinal area was followed by facilitation of the test response to fornix stimulation at many shock spacings. A "turnover" point in the hippocampal response to fornix stimulation was seen in the vicinity of the dentate pyramidal cells during progressive penetration of the hippocampal formation.

4. Interaction patterns were studied in the entorhinal area to paired shocks to widely separated points in the dorsal and ventral regions of the hippocampus. Significant differences were found in the extent of projections between these two parts of the hippocampus and the entorhinal area. Stimulation of the dorsal hippocampus was followed by large recruiting responses in the whole length of the entorhinal area. Stimulation of the ventral hippocampus was followed by entorhinal responses with much less evidence of recruitment. Stimulation of the entorhinal area was followed by smaller responses in the ventral hippocampus than in the dorsal, with fewer slow-wave trains in the ventral hippocampal responses.

5. Interaction studies suggest that an influx from the dorsal hippocampus can exercise a powerful influence over activity in the whole length of the entorhinal area. Although ventral areas of hippocampus do not appear similarly potent, the evidence suggests the presence of large projections between ventral and dorsal regions of the hippocampus through which the ventral hippocampus may exert its influence on patterns of intra-hippocampal integration.

6. Efferent projections from the entorhinal area to the midbrain tegmentum have been examined. The findings confirm previous histological studies (Adey, Merrillees and Sunderland, 1956) that a bilateral efferent pathway exists through the stria medullaris from the entorhinal area. Responses in it from entorhinal stimulation have many of the characteristics of a monosynaptic pathway, and exhibit a significantly shorter latency than those induced in the stria from hippocampal stimulation. The latency differences are compatible with the concept of a hippocampal projection to the stria medullaris through the entorhinal area. Responses in the midbrain at the intercollicular level were localized to the dorsal tegmentum in a region adjoining the periventricular gray matter where previous histological studies had suggested that fibers from the entorhinal area might terminate.

(Authors' Abstr.)

AUGUST

The Effect of Phenylephrine, Methamphetamine, Cocaine, and Serotonin Upon the Adrenaline-Sensitive Component of the Reticular Activating System

A series of sympathomimetic agents and related substances were tested for their effect upon the EEG and blood pressure of the unanesthetized cat with mid-reticular coagulation. Adrenaline, noradrenaline, and phenylephrine all produced prompt, short-lasting and reproducible EEG activation and rise in blood pressure, but showed certain quantitative differences. Methamphetamine produced a feeble direct effect upon the EEG and blood pressure, and both responses showed tachyphylaxis. Both methamphetamine and cocaine were able to lower the threshold to adrenaline EEG activation ten-fold or more, and in large enough cumulative doses produced a sustained EEG activation which was abolished by further destruction of the mesencephalic tegmentum. Serotonin produced alternate phases of EEG activation and deactivation dissimilar in pattern to that produced by the sympathomimetic agents.

It is postulated that the central nervous system stimulating properties of methamphetamine and cocaine observed clinically are due to their sensitizing effect upon an adrenergic component of the reticular activating system.

(Author's Abstr.)

VOL. 124 J. NERV. MENT. DIS. JULY, 1956

Studies on Hallucinogenic Snuffs. Physiologically Active Components

Examination of seeds of *Piptadenia peregrina* obtained from Puerto Rico showed that the principal alkaloid present was bufotenine, an indole compound closely related to serotonin. Bufotenine had never before been isolated from a plant source although it has been found in the skin glands of toads and in certain mushrooms. Later on, two samples of snuff, one from Venezuela and one from Colombia, were studied chemically; and, again, bufotenine was found to be present in large quantities. Since the seeds of *Piptadenia* sp. are the only presently known seed source of bufotenine, strong support for the claims of Safford was thus established. Paper chromatographic comparisons of extracts of the snuffs and seeds provided the analytical evidence.

Further chemical study of various seed extracts resulted in the isolation of additional organic bases closely related to bufotenine. One such source *Piptadenia macrocarpa* contained five related indole compounds: bufotenine, N,N-dimethyltryptamine, bufotenine oxide, N,N-dimethyltryptamine oxide, and a substance of unknown structure. Structural comparisons of these materials with serotonin, the powerful vasoconstrictor which has received much attention recently, and with tryptophan from which all are undoubtedly derived, bring up interesting pharmacological questions: What physiological action, if any, do these compounds have? How do the slight variations in structure affect activity? Work done at the National Heart Institute and elsewhere has indicated that bufotenine, N,N-dimethyltryptamine and serotonin all have grossly similar effects on the cardiovascular system of the dog and cat. No obvious central nervous system effects were observed in these animals at a low dose level. The oxides were much less active than the bases. In the studies of Dr. Edward Evarts of the National Institute of Mental Health, it was found that the effects of bufotenine in the monkey were very similar to those of LSD, and that bufotenine and N,N-dimethyltryptamine exhibited similar actions on the synaptic junction of the optic nerve of the cat at approximately equivalent dose levels.

It should be pointed out that pharmacological examination of other fractions of seed extracts has not, as yet, afforded any evidence that physiologically active agents other than the five indole compounds are present. This possibility must not be excluded, however, when one considers the frequent observations pertaining to species differences with respect to physiological activity, along with the fact that animals are not ideal subjects for the study of drug-produced psychoses. For example, in man, LSD is active at a dose level of 0·0003

mg./kg. In the monkey, doses of 1 mg./kg. of LSD and 3 mg./kg. of bufotenine are employed for producing profound behavioral disturbances. This difference is 10,000-fold.

Chemical, Enzymatic and Metabolic Studies

A great deal of work on the chemistry of these compounds has been in progress. It will be sufficient here to state only that some of these chemical studies were directed toward proof of structure of the indole components of the seeds and that others were directed, as closely as possible, to the duplication of enzymatic conditions. It was found in enzymatic work that some of the products obtained were identical with those previously isolated from chemical reactions. For example, the soluble and microsomal fraction of mouse liver homogenate converts N,N-dimethyltryptamine to its oxide. When the oxide is incubated with whole homogenate, some of it is reduced back to the parent amine. These same reactions were also carried out under mild chemical conditions. The mitochondrial fraction of mouse liver homogenate converts N,N-dimethyltryptamine to 8-indoleacetic acid. This is not an unexpected result when one considers the metabolism of bufotenine in man. When Dr. H. D. Fabing administered bufotenine (the 5-hydroxy analog of N,N-dimethyltryptamine) to convicts at the Ohio State Penitentiary, urine samples were collected and examined. It was found that a small fraction of the bufotenine was excreted unchanged, but the major portion was converted to and excreted as 5-hydroxy-3-indoleacetic acid. Since, as stated above, oxides of tertiary amines are formed by mammalian enzymes, the next step was to learn if these oxides would undergo an enzymatic reaction. Results with the oxides of bufotenine, and N,N-dimethyltryptamine have, so far, been negative. but it was found that the oxide of N,N-dimethyltryptophan, an amino acid oxide which was prepared synthetically, did undergo this type of reaction. One of the N-methyl groups was eliminated from the molecule. Another unidentified product was formed. In the latter case, carbon dioxide was lost from the molecule.

The results of these enzymatic experiments have led to the conclusion that a new sequence of tryptophan metabolism should be proposed for plants and possibly for mammalian organisms. The next step will be to learn if any of these compounds plays a vital role in normal or, perhaps, abnormal physiological processes.

(Authors' Abstr.)

An Examination of Phenothiazine Derivatives with Comparisons of their Effects on the Alerting Reaction, Chemical Structure and Therapeutic Efficacy

A series of phenothiazine derivatives was examined to determine the effect on the reticular formation. Three derivatives which failed to block the altering reaction to pain were inferior to chlorpromazine in the management of disturbed psychotic patients. It is therefore suggested that failure to depress the alerting reaction may be used as a screening procedure of new phenothiazine derivatives. But the converse does not hold, and their ability to inhibit alerting is not an adequate sign of therapeutic efficacy. In general, phenothiazine derivatives with 3 carbons in a straight chain are more effective tranquilizers than others with a greater or lesser number of carbons.

(Authors' Abstr.)

Behaviour of the Salamander Under the Influence of LSD-25 and Frenquel and Accompanying Electrical Activity of Brain and Spinal Cord

1. In the salamander, LSD-25 depresses the behavioural responses of touch, righting, swimming, walking, and vision, but the corneal response remains. During the peak of drug action the salamander assumes statue-like postures, and the electrical activity of the spinal cord shows a sustained discharge of waves of high frequency and amplitude.

2. Frenquel modifies the behaviour of the salamander by producing unsteadiness of gait, weakness of forelimbs, and a wobbly method of swimming. During the height of Frenquel action the electrical activity of both brain and spinal cord shows waves of very low amplitude.

3. With the dosages and methods used in this investigation, Frenquel and LSD-25 in some measure mutually modify the effects of one another. When the drugs are used together, they exert a depressant effect on behavioural responses and produce a weakened condition.

(Authors' Abstr.)

AUGUST

SEPTEMBER

VOL. 20 J. NEUR. NEUROSURG. PSYCHIAT. MAY, 1957

VOL. 16 J. NEUROPATH. EX. NEUR. APRIL, 1957

Neuropathological Study of Prefrontal Lobotomy

The brains of 7 cases of prefrontal lobotomy were studied histologically. Frontal lobe lesions caused degeneration and gliosis of the superior and inferior longitudinal fasciculi, the cingulate fasciculus, and the uncinate fasciculus as well as fronto-thalamic projection fibers and the dorsomedial thalamic nucleus. The superior longitudinal fasciculus is apparently a partially crossed pathway. A chronic demyelinization of the cerebral white matter apart from the above tracts was seen in 2 cases.

(Author's Abstr.)

JULY

JULY

VOL. 21 **J. PROJ. TECHN.** MARCH, 1957

JUNE

VOL. 22 **J. SPEECH HEAR. DIS.** JUNE, 1957

Variations in Consciousness Produced by Stimulating Reticular Formation of the Monkey

Stimulation of various areas in the reticular formation of the macaca mulatta produced a change in behaviour which the authors infer is due to a change in the state of consciousness. They believe such a change in consciousness is not dissimilar to that seen in humans experiencing an epileptic episode of either the petit mal or a psychomotor variant type.

(Authors' Abstr.)

JUNE

Functional Relationships Between the Red Nucleus and the Brachium Conjunctivum. Physiologic Study of Lesions of the Red Nucleus in Monkeys with Degenerated Superior Cerebellar Brachia

An attempt was made to determine the physiologic effects of localized lesions in the red nucleus in monkeys with complete and partial degeneration of the superior cerebellar peduncles. In ten rhesus monkeys portions of the deep cerebellar nuclei were removed by suction, and in one additional animal the brachium conjunctivum was completely sectioned caudal to the inferior colliculus. After observing these animals for periods of approximately 200 days, attempts were made to produce secondary stereotaxic lesions in the red nuclei. The latter procedures were successful in five animals. Serial sections of the brains and portions of the spinal cords were prepared by the Marchi method.

The following conclusions were drawn:

1. Lesions of the red nuclei in the monkey produce marked hypokinesis and increase the degree of hypokinesis associated with lesions of the deep cerebellar nuclei and the brachium conjunctivum.

2. In monkeys with complete or virtually complete degeneration of the brachium conjunctivum, lesions of the red nuclei do not significantly alter ataxia, ataxic tremor, or asynergic disturbances.

3. Lesions of the red nuclei may provoke an increase in ataxia and a reappearance of ataxic and simple tremor in monkeys with partial degeneration of the brachium conjunctivum, particularly if fibers in the dorsomedial portion of this structure have been preserved.

4. Transient choreiform activity may result from localized lesions of the red nucleus, but only if portions of the brachium conjunctivum are under-generated.

The hypothesis is presented that dyskinetic phenomena resulting from localized lesions of the red nucleus in the monkey are a consequence of interruption of ascending fibers of the brachium conjunctivum rather than destruction of the cells in the red nucleus.

(Author's Abstr.)

JULY

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